

## REMARKS

The claims have been amended to further define the invention. The isolated chamber of the instrument has a volume of less than 1.2 cubic millimeters, and a plurality of miniature biopsy sampling devices are included on a single catheter, e.g., 10, 20, 50, and up to hundreds of miniature sampling devices. In contrast to the cited prior art, the claimed method permits minimally invasive diagnostic procedures using picoliter to microliter volumes.

Claims 1-23 and 26-30 are pending. New claims 27-30 have been added; these claims are supported by disclosure at page 2, lines 12-15, and on page 5, lines 8-13, of the specification.

The Examiner has called attention to the term "abstracting" at page 3, line 20, of the specification and has requested rectification of an apparent typographical error. The entire sentence reads, "Also within the invention is a plurality of tissue sampling devices positioned on a catheter or needle for abstracting at least one tissue sample from a living subject." In this context, the word means to take away or remove (see Attachment A, dictionary definition for abstract). Accordingly, Applicants believe that correction is not required.

The drawings were objected to, because the lines were not of uniform thickness. To address the informality of the drawings, Applicants submit herewith formal drawings

No new matter has been added by this amendment.

### 35 U.S.C. 102

Claims 1-6, 8, 10, 12 and 17-19 were rejected for anticipation by Mosse et al., (WO 00/44285). Claims 1 and 17 have been amended to require that the volume of the isolated chamber be less than 1.2 millimeters. Mosse et al. fail to describe a chamber with the volume requirements of the amended claims. Withdrawal of this rejection is therefore requested.

### 35 U.S.C. 103

Claim 16 was rejected for obviousness over Mosse et al. The Examiner states:

Mosse does not expressly disclose that the volume of the isolated chamber ranges from 0.001 to 1 cubic millimeter. At the time the invention was made, it would have been an obvious matter of design choice to a person of ordinary skill in the art to make the volume of the chambers between 0.001 and 1 cubic millimeter because Applicant has not disclosed that this range of volumes provides an advantage, is used for a particular purpose, or solves a stated problem. One of ordinary skill in the art, furthermore, would have expected Applicant's invention to perform equally well with a different chamber volume because the instrument would still successfully obtain biopsy samples. Therefore, it would have been an obvious matter of design choice to modify Mosse to obtain the invention as specified in claim 16.

The device of Mosse et al. is an endoscope for taking multiple biopsies from the oesophagus in an oriented fashion (page 2, lines 13-18, of Mosse). As is well known in the art, an endoscope is a device used for examining visually the interior of a bodily canal or a hollow organ such as the esophagus, colon, bladder, or stomach. In this case, the endoscope is equipped with recesses for holding biopsies for the purpose of determining gross pathology of the margins of a precancerous/cancerous state known as Barrett's esophagus.

Segments of Barrett's esophagus may extend 3 to 10 centimetres or more above the gastroesophageal junction. Segments of Barrett's esophagus shorter than 3 cms used to be regarded as a normal finding at endoscopy but probably also have a risk of progression to cancer. It has been recommended that biopsies are taken from four quadrants of Barrett's oesophagus at either 1 or 2 centimetre intervals at alternate years for histological assessment to look for changes such as dysplasia which may predict or indicate the development of cancer. (page 1 of Mosse et al.)

Consistent with the use of Mosse's device, the reference states that the openings are somewhat smaller than the recesses, being typically 3 to 5 mm in diameter (page 5, lines 19-20 and Figs. 2a, 2b). Mosse et al. further state that a piece of tissue (mucosa and submucosa) nearest the surface of the oesophagus is drawn in. The recesses are made sufficiently shallow that deep muscle tissue is not drawn in (page 6, lines 18-20, of Mosse). The depth of the mucosal and submucosal tissue drawn in is on the order of millimeters (e.g., 3 mm; Lim et al, 1999, Dig. Dis. 17:145-152; Attachment B). Thus, the volume of the chambers is approximately an order of magnitude different from that of the claimed invention. (e.g., less than 1.2 cubic millimeters, 0.001 to 1 cubic millimeter).

The invention utilizes miniature biopsy sampling devices consistent with the goal of accomplishing a diagnosis in a minimally invasive manner. Unlike Mosse's device, which is used to map gross anatomical changes, the claimed sampling method interfaces with analytical tests that use a minimal amount of tissue per analytical procedure. The method of the invention provides distinct advantages as taught in the specification (page 5, lines 23-29).

For example, the analysis and examination of smaller tissue and/or fluid samples reduce the amount of tissue required per analytical procedure. Analytic methods, e.g., Polymerase Chain Reaction (PCR), are used to obtain diagnostic information. The instrumentation and sampling methods described herein permit the replication of genetic data from very small samples, eliminating the need for large tissue samples.

It would not have been obvious to modify Mosse's endoscope as now claimed, because the cited prior art does not describe the microminiaturization of sampling and analysis approach taught and claimed by the Applicant. In view of the claim amendments, clarifications provided above, and stated advantages of the claimed instrument, Applicants submit that claim 16 is nonobvious over the prior art. The remaining claims contain similar volume requirements and are nonobvious over Mosse et al. for the same reasons.

Claims 7, 20-23, and 26 were rejected for obviousness over Mosse et al. in view of Sorenson et al. (U.S. Patent No. 5,320,627). These claims require a heating element for actuating a mechanical portion of the sampling device to collect and retain a sample. The Examiner stated:

it would have been obvious to one having ordinary skill in the art at the time of invention to have used a heating element for causing actuation of a mechanical portion to collect and retain a biopsy sample as taught by Sorensen in place of the mechanical actuation of Mosse in order to achieve the predictable result of actuating a biopsy mechanism to obtain biopsy sample.

Sorenson merely describes a heating element and provides no addition description regarding the other novel and nonobvious elements of the invention as now claimed. As discussed above, the claims have been amended to clarify the size of the isolated tissue sample chamber and the method of obtaining numerous miniature tissue samples in a minimally invasive manner, thereby avoiding pain and trauma associated with removal of large tissue samples for diagnostic procedures. Applicants submit that these profound advantages are sufficient to overcome the articulated obviousness rejections and respectfully request withdrawal of these rejections.

### CONCLUSION

Applicant believes the amended claims are in condition for allowance, which action is respectfully requested. Applicant reserves the right to prosecute claims which are equal to or broader in scope in this or future applications related to the above-identified patent application.

Should the Examiner have any questions concerning the enclosure submitted herewith, the Examiner is invited to telephone the undersigned agent of record at the number provided.

The Commissioner is hereby authorized to charge any fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311 (Reference No. 26859-002).

Respectfully submitted,



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# Therapeutic Options in Patients with Barrett's Esophagus

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## Key Words

Barrett's esophagus · Intestinal metaplasia · Ablation therapy

## Abstract

The rising incidence of esophageal adenocarcinoma has focused attention on the only known risk factor: Barrett's esophagus. Practice guidelines for the diagnosis, surveillance and management of Barrett's esophagus were published recently. Although the ultimate goal in the management of this premalignant condition would be the permanent elimination of Barrett's mucosa, current therapeutic options are limited or still in the investigational stages. This review summarizes current medical and surgical treatment options and introduces endoscopic ablative modalities currently under investigation.

## Introduction

Over the past three decades, a striking threefold rise in the incidence of esophageal adenocarcinoma [1, 2] has focused attention on the only established precursor lesion: Barrett's esophagus. This attention has resulted in refinement of the diagnosis of Barrett's, and better, but still incomplete, understanding of the natural history of the metaplasia-dysplasia sequence in Barrett's epithelium. In addition, certain epidemiologic characteristics of the

population at risk for this premalignant condition are coming to light [3].

The diagnosis of Barrett's esophagus is now made when any length of columnar-lined epithelium (CLE) with intestinal metaplasia (IM) is present in the tubular esophagus [4]. Because this diagnosis is stricter in one aspect (the presence of IM and not simply columnar metaplastic cells) and looser in another (any length of CLE rather than  $CLE \geq 3$  cm) when compared to previous definitions, the incidence, prevalence and risk of dysplasia development must be reassessed.

A recent review of the epidemiology of the columnar-lined esophagus by Cameron [5] described a 3–5% prevalence of CLE in patients with reflux symptoms and a 1% prevalence of Barrett's esophagus in all patients undergoing upper endoscopy for any clinical indication. Studies using the newer diagnostic criteria estimate the prevalence of Barrett's at 12% for reflux patients in the community [3] and up to 48% for selected patient groups (Caucasians with reflux at a referral center) [6]. However, prospective population studies based on these new criteria are needed to determine the natural history and risk of dysplasia in CLE with IM of  $< 3$  cm or IM at the gastroesophageal junction.

Due to the potentially significant number of reflux patients at risk for Barrett's esophagus, the American College of Gastroenterology has proposed practice guidelines for endoscopic screening and subsequent surveillance based on the presence and grade of dysplasia [7]. Treatment recommendations in these guidelines offer

**Table 1.** Management strategies for Barrett's esophagus: treatment options

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Acid suppression in symptomatic patients
Reflux control with antireflux surgery in symptomatic patients
Endoscopic ablation of Barrett's mucosa
Surgical resection of high-grade dysplasia
Combination therapy

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antireflux therapy (medical or surgical) in patients with reflux symptoms and Barrett's esophagus with no or low-grade dysplasia, and advise esophagectomy versus continued surveillance in patients with high-grade dysplasia (HGD).

Recently, however, a new treatment modality, endoscopic ablation, has been developed which may cause regression or halt the progression of the metaplasia-dysplasia sequence in Barrett's esophagus. This review summarizes the effectiveness of current medical and surgical options (table 1) and introduces the endoscopic ablative methods currently under investigation.

### Medical Treatment

The medical management of Barrett's esophagus is controversial and has been aimed at controlling the reflux of acid into the esophagus. This can be achieved by using proton pump inhibitors or histamine-receptor antagonists to control symptoms and heal esophagitis. However, symptom control per se does not correlate with adequate control of acid reflux by esophageal pH monitoring in patients with or without Barrett's esophagus [8].

Multiple studies have demonstrated that acid suppression which effectively controls symptoms can lead to the appearance of squamous islands within columnar-lined epithelium but does not cause regression of Barrett's, i.e. a decrease in the overall length [9, 10]. Recent studies show that further escalation in drug doses, to achieve normal esophageal pH, does not seem to result in regression either. Of 27 patients with Barrett's esophagus on 60 mg of Lansoprazole for symptom control, 13 agreed to undergo ambulatory 24-hour pH monitoring while on therapy. Eight of the 13 patients had normalization of their esophageal pH, improvement in symptoms, and healing of esophagitis. Despite an increase in the number of squamous islands, the length of Barrett's esophagus did not change after an average of 5.7 years follow-up

[11]. This suggests that metaplasia itself may not be reversible or that elements other than acid may play a role in the development and maintenance of columnar metaplasia.

Furthermore, many patients with Barrett's esophagus may be found incidentally and have no symptoms of reflux to guide pharmacotherapy. Although the degree of acid reflux in patients with Barrett's rivals that of patients with esophagitis [12], the use of acid-suppressive medications in asymptomatic refluxers with Barrett's esophagus cannot be recommended at present. Since there are sparse data demonstrating either regression of Barrett's esophagus or a reduction in the risk of progression to dysplasia, the role of acid suppression in Barrett's should be symptom-based [7].

### Surgical Management of Barrett's Esophagus

#### *Antireflux Surgery*

The current indication for antireflux surgery is to provide long-term control of reflux symptoms. Its effectiveness in reducing acid in the esophagus is equivalent to acid-suppressive medications. Although it offers the added physiologic benefit of reducing esophageal exposure to the nonacid components of gastric refluxate, antireflux surgery has not been shown to cause regression of Barrett's. However, some studies suggest that it may play a role in altering or delaying the malignant progression of Barrett's.

In the only prospective study randomizing patients to medical vs. surgical therapy to date, after a median follow-up of 4.5 years, of 32 patients with Barrett's without dysplasia who received standard medical treatment or failed antireflux surgery, 7 showed dysplastic changes including 2 patients with severe dysplasia. The 27 patients who had successful and effective antireflux surgery (by clinical and pH criteria) did not develop any grade of dysplasia. It was also observed that the median length of the Barrett's mucosa was noted to decrease from 5 to 4.5 cm in the surgical group and increased from 4 to 5 cm in the medically treated group ( $p < 0.01$ ) [13]. However, this observation questions the clinical relevance and generalizability of change in length of Barrett's as a parameter of regression in clinical trials, particularly in light of the finding of Kim et al [14] that approximately 10% of patients had a change of  $\geq 4$  cm in the lower esophageal sphincter level on endoscopy and manometry between examinations.

Another prospective but nonrandomized study of Barrett's patients (presence of dysplasia on enrollment was

not stated) undergoing antireflux surgery found that esophageal cancer occurred only in the early postoperative years (longest screening time to finding cancer was 3.25 years) and not randomly over the follow-up years (median of 6.5 years, maximum of 18.2 years) [15]. This suggests that antireflux surgery may prevent the progression of Barrett's metaplasia to dysplasia. However, the impact of surgery on the progression of dysplasia to cancer cannot be determined from these data since the cancers may have been present preoperatively and the period of such progression may exceed 18 years.

Overall, the data from surgical series support the inference from trials of medical acid suppression that reflux may not be the pivotal factor in the maintenance or progression of Barrett's. Neither medical nor surgical control of acid reflux effectively induces the regression of Barrett's when assessed by a decrease in the length (or surface area) of CLE. But since different substances in the refluxate may be involved in the initial rather than the subsequent metaplastic-dysplastic mutagenic sequence, antireflux surgery may arrest the progression of Barrett's [16].

### Esophagectomy

Until recently, esophagectomy has been the standard of therapy for patients with Barrett's epithelium containing HGD or carcinoma in situ. This approach is based on surgical data demonstrating that esophagectomy specimens harbored unsuspected foci of cancer and even lymph node involvement in approximately 50% of patients with HGD [17–20]. In nonsurgical series, patients with HGD referred for esophagectomy from Barrett's surveillance programs had earlier stage tumors and better outcomes than nonsurveyed patients, and the prevalence of unsuspected adenocarcinoma was approximately 20% [21].

New information about the natural history of Barrett's suggests that the progression from HGD to cancer may take over 5 years. A recent abstract reported that 43 of 58 patients (74%) with HGD remained status quo histologically or regressed to less severe histology after a mean follow-up of 10 years [22]. The remaining 15 patients (26%) progressed to intra- or submucosal cancer. Another prospective series described 42 HGD patients under biopsy surveillance every 3–6 months. Although adenocarcinoma was detected in 8 patients as early as 9 months after HGD was found, the remaining 34 patients did not progress to adenocarcinoma over a mean follow-up of 7.5 years [23].

These insights into the HGD to cancer sequence from surveillance studies suggest that in patients with HGD and synchronous foci of cancer (usually detected within 1 year), esophagectomy is the treatment of choice. However, for a significant number of HGD patients who have no cancer detected for several years during close biopsy surveillance, or who have severe comorbidities, nonsurgical ablation may be a treatment option.

### Endoscopic Ablation of Barrett's Esophagus

One of the many new technical developments in endoscopy is ablative therapy. This form of minimally invasive destruction of mucosal lesions, benign or malignant, rests on the principle that the epithelium of the intestinal tract regenerates normally after injury. Furthermore, targeted injury of the luminal mucosa would presumably limit the risks of submucosal damage such as stricturing or perforation. Thus, this novel approach opens a new therapeutic option for Barrett's which, in contrast to medical or surgical therapy, can potentially induce the regression of Barrett's epithelium, prevent the progression of dysplasia and allow the regeneration of normal squamous mucosa in its usual milieu.

Current endoscopic ablative techniques under development include thermal, photochemical, ultrasonic and cryothermal methods and the experience to date is summarized below. Although each is technically feasible, the optimal parameters for ensuring complete ablation and minimizing complications in a practical manner are the subject of investigation at this time. Once these are determined and Barrett's epithelium or dysplasia can be effectively eliminated, antireflux surgery must be considered to prevent recurrence in the long term. It must be noted that all ablative treatments are carried out in conjunction with proton pump inhibition of gastric acid production or, more recently, antireflux surgery.

#### *Electrocautery and Laser (Thermal Ablation)*

Multipolar electrocoagulation (MPEC) to ablate Barrett's epithelium has been described in several small series. Sampliner et al. [24] documented complete reversal and regression of Barrett's epithelium with a mean length of 4.7 cm in 12 patients after an average of 6–7 sessions of MPEC. Follow-up for an average of 12 months showed no histologic or endoscopic recurrence in 10 patients [24]. Similarly, another study showed that 90% of the 21 study patients had complete elimination of the targeted Barrett's mucosa 1 year after treatment with MPEC. Multiple

sessions were also required, the number depending on the length of the Barrett's segment (average of 3.4 sessions for Barrett's of > 2 cm in length) [25]. Furthermore, this is a contact method requiring direct apposition of probe and mucosa for delivery of energy, hence, with in vivo variations of peristalsis, respiration, and insufflation, a variable depth of injury is seen and may lead to undertreatment (and residual subsquamous columnar cells) or overtreatment (and perforation or stricturing). The former has been reported in several cases of Barrett's ablation therapy, regardless of energy form. But the latter complications have not been reported with MPEC [24, 26]. The practical advantages of this method are the low cost of utilization, its widespread availability, and the familiarity of most endoscopists with the MPEC technique.

Attempts to thermally ablate Barrett's mucosa with different lasers (KTP, argon and Nd:YAG) have also been investigated. The KTP laser has several advantages over other types of lasers; it offers superficial coagulation and variable depth effect when the pulse duration is adjusted and, furthermore, is a noncontact technique which allows a free-hand, paintbrush-like manner. Two studies using KTP ablation, one in 16 patients without dysplasia [25] and another in 10 patients with dysplasia or early adenocarcinoma [27], demonstrated that squamous regeneration is possible but complete reversal of Barrett's (endoscopic and histologic) was achieved in only 12.5 and 80% of patients respectively, due to persistence of residual subsquamous intestinal metaplasia. The variability in response is attributable to differences in power settings, session frequency and intensity of proton pump inhibition between the two trials.

Similar data exist for other types of lasers including the argon laser and Nd:YAG laser [28-31]. For example, in one series, 10 patients underwent ablation of only half of the circumference of their Barrett's (average of 3 sessions) with an argon laser while on acid suppression medication. Areas that were ablated showed partial or complete regeneration of squamous mucosa that was not observed in control nonablated locations. Follow-up ranged from 6 to 38 weeks [28]. Laser ablation with non-contact Nd:YAG is limited to a case report [29] and a small randomized trial with 4 patients in each arm which showed no difference in the Barrett's length 6 months after ablation [30].

In a novel and rational approach, a Finnish group performed contact Nd:YAG ablation of Barrett's after antireflux surgery, thus ensuring the absence of any injurious refluxate in the healing esophagus. Eleven of 17 postsurgical patients who agreed to participate underwent

a mean of 4 treatments 3 months apart. Although 2 of the 11 had residual intestinal metaplasia at the gastric cardia, none was detected over the next 2 years in the remaining patients. As expected, there was no change in the length of Barrett's in the control group who had refused ablation.

#### *Argon Plasma Coagulation*

Argon plasma coagulation (APC) is a technique that delivers controlled monopolar electrocoagulation via a stream of ionized argon gas ignited by a high voltage discharged at the tip of a specialized flexible probe. It is a noncontact ablative method with a predetermined depth of injury (approximately 2 mm) that is most often used for coagulation of bleeding surface lesions such as arteriovenous malformations.

Many studies of APC ablation in Barrett's were reported in 1998. Each has demonstrated variable success in the sustained restoration of normal squamous epithelium in Barrett's. In one study 15 of 21 patients (70%) with Barrett's mucosa without dysplasia had normal mucosa restored 8 months after ablation with APC [32]. In another study, of 25 patients with Barrett's esophagus without HGD who underwent ablative therapy with APC, 15 patients (60%) had some response but only 8 patients (32%) achieved complete endoscopic and histologic restoration and 2 patients (8%) had no response at all [33]. Another small study confirmed the above findings where 3 of the 8 study patients still had intestinal metaplasia by biopsy after therapy was completed [32].

In the largest APC ablation study to date, 30 patients (4 low-grade dysplasia, 3 HGD) with Barrett's of > 3 (median 5, range 3-17) cm were treated [35]. Successful response was defined as residual CLE of < 2 cm. All 27 patients who completed treatment had a macroscopically successful response over a median follow-up of 9 months including 2 patients with HGD who had both endoscopic and histologic return to squamous epithelium at 1 year. The restoration of squamous epithelium in 4 patients with persistent reflux symptoms was only achieved after doubling the omeprazole dose to 40 mg/day.

However, as in the previously cited studies, a significant 30% of patients continued to have subsquamous intestinal metaplasia. Whether these residual areas of Barrett's have the same risk of progression to dysplasia postablation is not clear and, therefore, continued biopsy surveillance of all ablated segments is mandatory. This study also reports the first instance in any Barrett's ablation experience of perforation and subsequent death, both occurring relatively early in the trial. These types of complications,

undertreatment with residual Barrett's and overtreatment with resultant perforation or possibly stricturing, underscore the technical challenges of endoscopic thermal ablation in terms of depth of injury and operative skill.

#### *Photodynamic Therapy*

Photodynamic therapy (PDT) has received much attention and holds much promise as a therapeutic option in patients with HGD and early esophageal cancer. This form of noncontact nonthermal ablative therapy involves the in situ photoactivation of an otherwise nontoxic drug, a photosensitizer, which has accumulated in tumor and normal tissues following oral or intravenous administration. The photosensitizer is activated by a wavelength of light that matches the absorption spectrum of the drug. The resultant photochemical reaction gives rise to highly active singlet oxygen species capable of causing cell death directly and a necroinflammatory cascade indirectly. Ideally, this effect selectively destroys only abnormal cells because the photosensitizer accumulates preferentially in the dysplastic or neoplastic cells and because only the target mucosa is illuminated during a treatment session.

Currently, in the USA, the only approved sensitizer is porfimer sodium (Photofrin®), a hematoporphyrin derivative, for the palliation of obstructive esophageal cancer. The technique of PDT for this indication involves administration of porfimer sodium intravenously followed by delivery of 630 nm light generated by a laser 48 h later using a cylindrical diffuser or a windowed centering esophageal balloon. The same technique is used for treating Barrett's esophagus, but may vary slightly with other photosensitizers. There is a 4- to 6-week period of skin photosensitivity after Photofrin® administration.

For the palliation of obstructive esophageal cancer, the effectiveness of PDT equals that of Nd:YAG laser therapy [36]; but there is hope for its application in HGD and intramucosal carcinoma as a curative ablative modality due to an approximate depth of injury of 3 mm. The first encouraging results were reported in 1995 in 123 nonsurgical candidates with early squamous or adenocarcinoma of the esophagus [37]. PDT achieved a high rate of complete tumor response at 6 months (87%) in small (0.5-4 cm in diameter and T1 or T2 stage) esophageal tumors. Recurrences detected at a superficial stage after complete initial destruction responded to additional PDT.

Based on these promising results in early esophageal cancers, Overholt et al. [38, 39] used Photofrin PDT in 100 patients with Barrett's esophagus with dysplasia or superficial cancer (T1 or T2). During a follow-up of 4-84 (mean 19) months, Nd:YAG laser ablation was also per-

formed in 84 patients to destroy small residual areas of Barrett's mucosa and omeprazole 20 mg b.i.d was given. Barrett's was completely eliminated by biopsy in 43% of patients (including 4 or 12 patients with T1 adenocarcinoma). Dysplasia was cleared in 78 of the 100 patients, and 10 of the 13 superficial cancers were eliminated. Those with persistent dysplasia (9%) either remained status quo or had a regression in their dysplasia grade.

Although no perforations occurred, these impressive responses were accompanied by esophageal strictures in 34% of patients as well as moderate chest pain and dysphagia requiring intravenous fluids in most. Of special concern is the development of dysplasia in segments of Barrett's not treated with PDT and the progression of subsquamous Barrett's to HGD or cancer in 3 patients at 6, 18 and 22 months after PDT.

Recent studies with a newer photosensitizing agent, 5-aminolaevulinic acid (ALA), appeared to show similar responses with better tolerance, lesser complications and several advantages [40, 41]. First, ALA is more rapidly eliminated from the body and hence decreases the duration of photosensitivity from several weeks to a couple of days. Second, it accumulates preferentially in the mucosa and not in submucosa. This offers more selective superficial damage limiting the risk of strictures and perforation. Third, ALA may have more tumor selectivity [40] and finally, it can be given orally.

In the largest series to date, Gossner et al. [42] treated 32 nonsurgical candidates with HGD (n = 10) or mucosal cancer (n = 22) using ALA as the photosensitizer in PDT. Histologic eradication was achieved in all HGD as well as adenocarcinomas of <2 mm thickness [42]. Far fewer complications were noted than with porfimer sodium; no stricturing was induced because the depth of injury is limited to the mucosa and the photodynamic inflammatory cascade does not affect the submucosa. The only complications mentioned in this study were transient nausea and asymptomatic mild transaminases elevations. Since the follow-up was limited (ranging from 1 to 30, mean of 9.9 months), the durability of the ablation is unknown. However, 2 cases of subsquamous columnar islands were noted on follow-up.

The advent of PDT has demonstrated the feasibility of ablating dysplastic mucosa and even early cancers of the esophagus in a more complete manner than thermal or APC ablation. This technique will be further refined by improving the precision and uniformity of light delivery to targeted areas and by the development of more tissue selective and specific photosensitizers with reduced photosensitivity periods.

### *Ultrasonic Energy*

This mechanical ablative method utilizes ultrasonic energy to injure epithelial cells without damaging muscle or stromal cells. In the only study to date, a Cavitron Ultrasonic Surgical Aspirator, was placed directly on the esophageal mucosa of pigs through a standard percutaneous gastrostomy. Ultrasonic energy was delivered to the circumference of the esophagus and the ablated tissue aspirated for cytologic analysis [43]. Complete ablation of epithelium superficial to the muscularis mucosa was achieved in one session without stricture formation. The current limitation of this technique is that the ultrasonic energy must be delivered through a rigid system, thus, its practical role in ablating Barrett's epithelium may be limited to application during antireflux surgery.

### *Cryotherapy*

Cryotherapy has been used to ablate tissues in solid organs such as the liver, but new flexible delivery systems have allowed endoscopic experimentation in hollow organs. A catheter spray system to deliver liquid nitrogen was used in an animal model to freeze the esophageal epithelium and resulted in targeted cell death by formation of ice crystals intra- or extracellularly. Cellular damage can either be caused indirectly as a result of osmotic shifts between tissue compartments, or directly by mechanical damage from ice crystals. However, because the degree and depth of mucosal damage could not be adequately controlled in this pilot study, one stricture and one perforation occurred in the 16 animals [44]. Pilot clinical trials are underway.

### *Summary of Ablative Methods*

Endoscopic ablative therapy appears to be a promising, feasible and novel approach to treatment of Barrett's esophagus. Until efficacy and effectiveness have been demonstrated, this therapy is most appropriately performed in a research setting for patients with HGD or early superficial cancer who are not surgical candidates. It is minimally invasive, superficial and carries less morbidity than surgery, but has the potential to cure a patient with mucosal neoplasia of the esophagus. For patients with low-grade or no dysplasia and operable patients with HGD, at this time, ablative therapy can only be undertaken in clinical trials with the understanding that although current ablative modalities appear to cause regression, their impact on the risks of progression are unknown.

Several issues still need to be addressed concerning the use of any ablative method. At the forefront are technical issues regarding the optimal depth of injury, the con-

**Table 2.** Management strategies for Barrett's esophagus in 1999 based without dysplasia status

Barrett's without dysplasia
Symptom control <sup>1</sup> and surveillance biopsies
Low-grade dysplasia
Symptom control <sup>1</sup> and surveillance biopsies
Endoscopic ablation, antireflux surgery, surveillance biopsies <sup>2</sup>
High-grade dysplasia/adenocarcinoma confined to mucosal (stage T1)
Esophagectomy
Endoscopic ablation, antireflux surgery, surveillance biopsies in the nonsurgical candidate <sup>2</sup>

<sup>1</sup> Medical or surgical.

<sup>2</sup> In research trials only.

trolled and uniform delivery of the ablative energy, and the ease and cost of its delivery. These factors will determine the efficacy of endoscopic ablation in terms of its completeness and durability. Until a form of ablative therapy is shown to restore normal squamous epithelium in the entire segment of Barrett's without residual submucosal columnar islands, assessing the completeness of ablation will entail continued endoscopic biopsy surveillance for an indefinite period. This surveillance will be complicated by the absence of endoscopically recognizable features of Barrett's.

Furthermore, given the long natural history of Barrett's development, measuring the durability of ablative therapy will be difficult and probably dependent on the effectiveness of antireflux measures. It can be argued that ablative therapy for Barrett's should always be followed by antireflux surgery for definitive management.

### **Conclusion**

In summary, although a number of ablative treatment options for Barrett's esophagus have appeared, the long-term effectiveness of these modalities and the unclear natural history of this condition precludes the recommendation of any one specific treatment modality. Until we can clearly define the subgroup of patients who possess the definite risk of malignant progression, choosing any one ablative option will require investigation and careful weighing of risks and benefits based on a patient's dysplasia status (table 2). The risk of undertreatment and possible subepithelial progression to cancer beyond a curative window must be balanced against overtreatment and sub-

**Table 3.** Comparison of current treatment modalities for Barrett's esophagus

Treatment	Availability	Advantages	Disadvantages	Outcome
Medical treatment	Widespread	Noninvasive	Ineffective pH control in many patients	Squamous islands, no regression
Antireflux surgery	Widespread	Possible to reduce risk of malignancy	Morbidity and mortality	Squamous islands, no regression
Esophagectomy	Widespread	Remove source of malignant potential	Morbidity and mortality	Favorable in early cancer (cure)
Ablative treatment				
MPEC	Widespread	Common technique, no reported complications	Contact therapy, multiple sessions, variable injury	Complete regression with subsquamous islands
LASER	Limited	Common, noncontact, no reported complications	Variable injury, multiple sessions	Complete regression with subsquamous islands
APC	Some centers	Noncontact, technically simple	Variable injury, multiple sessions	Complete regression with subsquamous islands
PDT	Limited	2 sessions per treatment	Photosensitivity and stricturing	Favorable in early cancer
Ultrasonic treatment (animal)	Very limited	One session per treatment	Rigid instrument, operative procedure	Complete regression
Cryotherapy (animal)	Very limited	Noncontact	Variable injury	Unclear

jecting patients to unnecessary and potentially dangerous treatments. Development of specific biological markers that can predate malignant changes in Barrett's [43], and the more sensitive endoscopic assessment of Barrett's mucosa with techniques such as light-induced fluorescence

endoscopy [46, 47] should improve the stratification of treatment options. In the meantime, the management of patients with Barrett's esophagus can be based on a combination of symptom control and appropriate referral to research centers for trials of endoscopic ablation (table 3).

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